REMARKS

Claims 1, 2, and 39-41 are pending. In the December 10, 2009 action, claims 1 and 39-41 are finally rejected under 35 U.S.C. § 103(a) as being unpatentable over Van den Heuvel et al., Am J Hum Genet. 62:262-268, 1998 ("Van den Heuvel") in view of U.S. Patent No. 6,040,138 ("Lockhart"). Claims 1, 2, and 39-41 are finally rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Application Publication No. 2006/0099578 ("Wallace"), as evidenced by U.S. Patent No. 5,494,794 ("Wallace '794"), in view of Van den Heuvel and Smeitink, Bioessay 23:518-525, 2001 ("Smeitink") and U.S. Patent Application Publication No. 2008/0187911 ("Papaconstantinou"). Each of these rejections is addressed below.

Claim amendments

Claim 1 has been amended to delete the phrase "at least two." No new matter is added by this amendment. Because this amendment merely clarifies the claim language as suggested by the Office, consideration and entry of this amendment is respectfully requested.

The invention

The present invention is based on the discovery that patients suffering from bipolar disorder exhibit lower expression of nuclear genes that encode polypeptides of complexes I-V of the mitochondrial respiratory chain, as compared to normal controls. The present claims are therefore directed to microarrays where at least 90% of the nucleic acids are nuclear genes that encode polypeptides of complexes I-V or are fragments thereof. The requirement that 90% of the nucleic acids are nuclear encoded genes means that at least some mitochondrial genes, which also encode proteins of complexes I-V, are excluded from the microarray.

Interview summary

The undersigned thanks Examiners Salmon and Nguyen for the helpful telephonic interview on March 15, 2010. In the interview, the rejections under 35 U.S.C. § 103(a) were discussed, as were possible claim amendments. The Office made the specific suggestion that the deletion of the phrase "at least two" from claim 1 may overcome the § 103(a) rejections.

In making this suggestion, the Office took the position that the wording of claim 1 left open the possibility that the claimed microarray could contain additional nucleic acids beyond those explicitly recited in the claim and indicated that the obviousness rejections were being maintained on the basis of this interpretation. In particular, the Office suggested that a "microarray consisting of *at least two* nucleic acids" could contain additional nucleic acids beyond the "at least two nucleic acids" and that those additional nucleic acids would not be subject to the limitations subsequently recited in the claim. To address this matter, the Office suggested that deletion of the phrase "at least two" would make it clear that all of the nucleic acids of the microarray would subject to these limitations.

Although Applicants believe the prior claim language to be clear on this point, claim 1 has nonetheless been amended to recite "a microarray consisting of nucleic acids, at least 90% are which are either (a)...or (b)...." In view of this amendment, Applicants believe that the Office's concern regarding the claim language has been rendered moot.

Rejection under 103(a) - Van den Heuvel in view Lockhart

Claims 1 and 39-41 are rejected as being obvious over Van den Heuvel in view of Lockhart. In making this rejection, the Office cites Van den Heuvel as teaching identification of a mutation in the human nuclear gene encoding the 18 kD (AQDQ) subunit of the mitochondrial respiratory chain complex I. Lockhart is cited as teaching placing nucleotides onto an array and measuring expression. Based on these teachings,

the Office concludes that it would have been *prima facie* obvious to bind the nuclear gene associated with the mutation taught by Van den Heuvel to the array taught by Lockhart, thus arriving at the present invention. Applicants respectfully disagree, for the reasons of record and as set forth below.

To find a claim obvious, "there must be some articulated reasoning with some rational underpinning to support a legal conclusion of obviousness." *KSR v. Teleflex,* 550 U.S. 398, 418; 82 U.S.P.Q.2d 1385, 1396. As neither Van den Heuvel nor Lockhart provides a reason for one of skill in the art to make the claimed array, these references cannot render claims 1 and 39-41 obvious.

Van den Heuvel describes identification of a single mutation in a single nuclear gene (AQDQ) encoding a protein of complex I in a patient suffering from a defect in mitochondrial respiration. This reference is focused on defects in mitochondrial respiration and on identification of mutations that cause such defects, be they mutations in nuclear or mitochondrial genes. Indeed, because Van den Heuvel teaches only a single mutation in a single nuclear gene, there is no reason provided to make a microarray at all. Even if it could be said that Van den Heuvel provides motivation to make a microarray, there is no reason one would consider making a microarray that necessarily omits at least some mitochondrial-encoded genes of complexes I-V, given the focus of this reference on mitochondrial respiration.

Lockhart fails to overcome the deficiency of Van den Heuvel. While Lockhart generally teaches arrays, this reference fails to provide a specific teaching that would lead one to a microarray of claims 1 and 39-41. Specifically, Lockhart fails to teach genes encoding the mitochondrial respiratory chain at all and provides no suggestion to generate the claimed microarray.

Thus, neither of these references provides a reason to make a microarray where 90% of the nucleic acids are nuclear genes encoding polypeptides of complexes I-V or are

fragments thereof. Claims 1 and 39-41 therefore cannot be obvious over Van den Heuvel in view of Lockhart, and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a) – Wallace in view of Smeitink and Papaconstantinou

The Office also rejects claims 1, 2, and 39-41 as being unpatentable over Wallace, as evidenced by Wallace '794, in view of Smeitink and Papaconstantinou. In making this rejection, the Office cites Wallace as teaching a microarray consisting of probes for mitochondrial genes, including genes drawn to mitochondrial energy. Smeitink is cited as teaching that the percentage of patients with mitochondrial DNA (mtDNA) abnormalities is relatively low and that screening for common mtDNA mutations in patients with an established oxidative phosphorylation disorder is unsatisfactory. Papaconstantinou is cited as teaching a microarray from which mtDNA genes were removed. Based on these teachings, the Office concludes the microarrays of claims 1, 2, and 39-41 to be obvious. This rejection is traversed for the reasons already of record and as set forth below.

These references fail to provide a reason to make a microarray that includes nuclear genes of complexes I-V but excludes at least some mitochondrial genes, as required by claim 1 and its dependent claims. The primary reference, Wallace, describes arrays for studying mitochondrial function, in which both nuclear and mitochondrial genes are involved (see paragraph 17). Wallace thus provides no reason to design a microarray focused on nuclear genes at the expense of mitochondrial genes. Indeed, no reason to design a microarray where at least 90% of the nucleic acids are nuclear genes that encode polypeptides of complexes I-V or are fragments thereof is provided.

This failure is not remedied by Smeitink or Papaconstantinou. Smeitink focuses on mitochondrial deficiencies, particularly on defects in oxidative phosphorylation (complexes I-V), and makes it clear that such defects can result from mutations in nuclear or mitochondrial DNA. See, for example, Figure 2 on page 523. This reference, like Wallace, also suggests that both nuclear *and* mitochondrial DNA should be analyzed.

Smeitink thus does not provide a reason to produce a microarray that excludes at least some mitochondrial genes and thus would not lead one to produce the claimed microarray.

Papaconstantinou, like Wallace, focuses on mitochondrial function in general and suggests something quite different from the array of the present invention, i.e., that *all* factors involved in mitochondrial function should be studied. There is no specific focus on nuclear genes encoding polypeptides of complexes I-V, as this reference states that the disclosed arrays "encompass all the factors that will affect mitochondrial biogenesis and assembly (replication) and mitochondrial function under any physiological or pathophysiological conditions." Papaconstantinou, page 4, paragraph 45. This reference thus provides no reason to make a microarray where 90% of the nucleic acids are nuclear genes encoding polypeptides of complexes I-V of the mitochondrial respiratory chain or are fragments thereof.

Taken together, none of Wallace, Smeitink, and Papaconstantinou provides a reason to make a microarray of claims 1, 2, and 39-41. Withdrawal of the § 103(a) rejection over these references is therefore requested.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Submitted herewith is a Petition to extend the period for replying to the final Office action for one (1) month, to and including April 10, 2010 and authorization to charge Deposit Account No. 03-2095 in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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